Sleep Medicine 15 (2014) 1362–1369

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Periodic leg movements during sleep in children scheduled for adenotonsillectomy: frequency, persistence, and impact

Ronald D. Chervin [a,*], Seockhoon Chung [b,c], Louise M. O'Brien [d], Timothy F. Hoban [e], Susan L. Garetz [f], Deborah L. Ruzicka [a], Kenneth E. Guire [g], Elise K. Hodges [h], Barbara T. Felt [i], Bruno J. Giordani [h], James E. Dillon [j]

[a] Sleep Disorders Center and Department of Neurology, University of Michigan, Ann Arbor, MI, USA
[b] Sleep Disorders Center, University of Michigan, Ann Arbor, MI, USA
[c] Department of Psychiatry, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea
[d] Sleep Disorders Center and Departments of Neurology, Oral and Maxillofacial Surgery, and Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI, USA
[e] Sleep Disorders Center and Division of Pediatric Neurology, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA
[f] Sleep Disorders Center and Division of Pediatric Otolaryngology, Department of Otolaryngology and Head and Neck Surgery, University of Michigan, Ann Arbor, MI, USA
[g] Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, MI, USA
[h] Division of Neuropsychology, Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA
[i] Division of Child Behavioral Health, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA
[j] Department of Psychiatry, Central Michigan University, Mount Pleasant, MI, USA

ARTICLE INFO

Article history:
Received 14 March 2014
Received in revised form 9 May 2014
Accepted 11 May 2014
Available online 6 June 2014

Keywords:
Periodic leg movements
Periodic limb movement disorder
Sleep apnea, obstructive
Polysomnography
Child
Arousals
Cognition
Sleepiness

ABSTRACT

Objective: The aim of this study was to assess the frequency and potential clinical impact of periodic leg movements during sleep (PLMS), with or without arousals, as recorded incidentally from children before and after adenotonsillectomy (AT).
Methods: Children scheduled for AT for any clinical indications who participated in the Washtenaw County Adenotonsillectomy Cohort II were studied at enrollment and again 6 months thereafter. Assessments included laboratory-based polysomnography, a Multiple Sleep Latency Test (MSLT), parent-completed behavioral rating scales, neuropsychological testing, and psychiatric evaluation.
Results: Participants included 144 children (81 boys) aged 3–12 years. Children generally showed mild to moderate obstructive sleep apnea (median respiratory disturbance index 4.5 (Q1 = 2.0, Q3 = 9.5)) at baseline, and 15 subjects (10%) had at least five periodic leg movements per hour of sleep (PLMI ≥ 5). After surgery, 21 (15%) of $n = 137$ subjects who had follow-up studies showed PLMI ≥ 5 ($p = 0.0067$). Improvements were noted after surgery in the respiratory disturbance index; insomnia symptoms; sleepiness symptoms; mean sleep latencies; hyperactive behavior; memory, learning, attention, and executive functioning on NEPSY assessments; and frequency of attention-deficit/hyperactivity disorder (DSM-IV criteria). However, PLMI ≥ 5 failed to show associations with worse morbidity in these domains at baseline or follow-up. New appearance of PLMI ≥ 5 after surgery failed to predict worsening of these morbidities (all $p > 0.05$), with only one exception (NEPSY) where the magnitude of association was nonetheless negligible. Similar findings emerged for periodic leg movements with arousals (PLMAI ≥ 1).
Conclusion: PLMS, with and without arousals, become more common after AT in children. However, results in this setting did not suggest substantial clinical impact.

1. Introduction

A periodic leg movement index (PLMI, number per hour of sleep) and a periodic leg movement arousal index (PLMAI) are required data on sleep study reports [1]. Yet, the meaning and clinical implications of periodic leg movements during sleep (PLMS) and PLMS with arousals, usually found incidentally during studies ordered

Support: National Institutes of Health (HL080941, HL105999).
* Corresponding author at: Ronald D. Chervin, Michael S. Aldrich Sleep Disorders Laboratory, C728 Med Inn, Box 5845, 1500 East Medical Center Drive, Ann Arbor, MI 48109-5845, USA. Tel.: +734 647 9064; Fax: +734 647 9065.
E-mail address: chervin@umich.edu (R.D. Chervin).

http://dx.doi.org/10.1016/j.sleep.2014.05.004
1389-9457/

for other indications, remain poorly understood and at risk for misinterpretation. In no age group is this lack of existing knowledge more notable than among children.

Although PLMS commonly occur in both adults and children with restless leg syndrome, or Willis Ekbom disease, and in fact can help to confirm this diagnosis, PLMS are most frequently encountered in the sleep studies of patients evaluated for suspected obstructive sleep apnea (OSA). Among adults who undergo laboratory-based polysomnography for this indication, the presence of PLMS does not predict increased risk for excessive daytime sleepiness, and in fact – especially when the PLMS are associated with arousals – it actually predicts slightly less sleepiness than seen in adults without PLMS [2,3]. Among children, data on PLMS and sleepiness are not available, but PLMS are reported to be especially common among children with attention-deficit/hyperactivity disorder (ADHD) [4,5], and a high proportion of children with PLMS are in turn reported to have ADHD [6–8]. The PLMS in children, perhaps because of associated arousals, have been hypothesized to contribute to ADHD and hyperactive behavior more generally.

If PLMS are associated with hyperactive behavior, then some understanding of the role that PLMS may play in pediatric OSA would be useful, as would an understanding of how PLMS evolve after adenotonsillectomy (AT) for OSA. Among adults, treatment of OSA, usually during an initial titration of positive airway pressure, has been reported to increase PLMS [9], decrease PLMS with arousals [10], have no overall effect [11], or have variable effects depending on apnea severity [12]. A decrease in PLMS might be hypothesized to occur if PLMS arise in part as a reaction to disrupted sleep, subtle hypopneas, or some other feature provoked by untreated OSA; conversely, an increase in PLMS conceivably could be understood as a release phenomenon whereby untreated apneic events mask or temporarily relieve an underlying drive for expression of PLMS [12]. In children, one study of 44 snoring children awaiting AT, at baseline and 6 months later, showed only a nonsignificant increase in PLMI, from a median of 1.7 to 2.3 [13]. Another study of 25 children with OSA, before and after treatment (mainly with positive airway pressure), suggested that PLMS diminish after sleep apnea is treated [14]. Whether the children were tested during their first titration night, on positive airway pressure, is not clear.

Amid this uncertainty, we took advantage of data collected in the Washtenaw County Adenotonsillectomy Cohort II [15,16] to study the frequency, persistence, and clinical impact of PLMS and PLMS with arousals among children, before and after AT performed for clinical indications. Although these subjects cannot shed light on the much smaller numbers of patients referred specifically for restless leg syndrome or periodic limb movement disorder, the sample is well suited for testing several hypotheses. We sought to confirm and quantify the frequency of PLMS among these children at high risk for sleep apnea; assess whether PLMS increase after AT; and examine whether PLMS or PLMS with arousals may contribute to insomnia, sleepiness, inattention, hyperactive behavior, or ADHD.

2. Methods

2.1. Overview

Subjects were recruited from the two largest otolaryngology groups in Washtenaw County for this institutional review board (IRBMED)-approved study. Clinical staff helped to identify families with children, aged 3.0–12.9 years, who were scheduled for AT for any clinical purposes, but were not judged to require sleep studies prior to the procedure as is most often the case [17]. Exclusion criteria have been detailed previously [15]. They included medical, mental, or physical conditions that might hamper interpretation of electroencephalography (EEG) or neurobehavioral findings; otolaryngologists' need for preoperative polysomnographic data; current or past treatment for OSA; medical conditions or syndromes that carry high risk for OSA or daytime sleepiness; or imminent expectation of further surgery or family relocation. For the current analyses, data were included from any cohort participant who underwent AT and had complete baseline polysomnography, with a total sleep time >6 h, and next-day multiple sleep latency tests.

A parent signed a written informed consent, and each child assented to participate. Sleep and neurobehavioral assessments were then completed up to 3 days before the AT and again 6 months after surgery. A child psychiatrist, child psychologist, or behavioral/developmental pediatrician conducted a structured interview with each family. A full laboratory-based polysomnogram was followed on the next day by a Multiple Sleep Latency Test (MSLT). Between naps, children underwent neuropsychological testing. A parent completed behavioral rating scales and a standard socioeconomic survey [18]. After each of the two major testing visits, children received a $25 gift certificate to a local toy store and parents received $125 for their time and effort.

Pediatric polysomnography for this study conformed to standard recommendations [19], published after this study began, except that piezoelectric strain gauges, rather than inductance plethysmography, were used to monitor thoracic and abdominal excursion [15]. Esophageal pressure was monitored through a water-filled, 6-French pediatric feeding tube [20,21]. Leg movements were monitored in each leg independently, using two surface electromyography leads, one over each anterior tibialis muscle. MSLTs followed standard recommendations [22], with two exceptions to better accommodate these young volunteer research subjects: four naps were performed instead of five, and nap opportunities were lengthened from the adult standard (20 min) to 30 min [23,24].

2.2. Scoring

All sleep studies were scored, or in a minority of instances, thoroughly rescored, by a single sleep and electroencephalography-registered technologist with extensive experience in pediatric polysomnography. To prevent bias and minimize any effect of scoring drift with time, all scoring was performed in batches that each contained the presurgical and postsurgical studies of several subjects, all de-identified, and without access to other study measures. Sleep staging followed recommended criteria [19]. Periodic leg movements and arousals were scored according to standard criteria as well, and were considered to be associated with each other when <0.5 seconds separated the end of one event and the onset of the other [19]. The PLMI and PLMAI were defined as the number of PLMS and PLMS with arousals, respectively, per hour of recorded sleep. Obstructive apneas of two or more respiratory cycles in duration, hypopneas, respiratory effort-related arousals (RERAs), and central apneas were scored according to criteria recommended for children by the American Academy of Sleep Medicine (AASM) in 2007 [19]. The respiratory disturbance index was calculated as the number of the above events per hour of sleep. In MSLTs, the mean sleep latency across all nap opportunities provided an objective measure of daytime sleepiness [25].

2.3. Subjective insomnia and daytime sleepiness

The Pediatric Sleep Questionnaire was administered to parents before and after AT. This commonly used instrument contains three items that ask about "difficulty falling asleep at night," "waking up more than twice a night on average," and "trouble falling back asleep if he or she wakes up at night." These items have face validity as assessments for difficulties with sleep initiation or maintenance that define the core features of insomnia [26] or sleeplessness in

children [27], and have proven useful in previous research [28,29]. The Pediatric Sleep Questionnaire also contains a well-validated 22-item Sleep-Related Breathing Disorder Scale [30,31], with a 4-item sleepiness subscale that itself has been validated as predictive of both OSA and MSLT results in children [30,32]. The 3-item insomnia subscale and 4-item sleepiness subscale were used as subjective assessments in the current study. The parent, with help from the child when necessary, answered each item as "Yes," "No," or "Don't Know." One or more endorsed symptom was used to identify children who, in comparison to their peers, were more likely to have subjective insomnia or sleepiness.

2.4. Neurobehavioral outcomes

Standardized and well-validated instruments were employed to identify DSM-IV diagnoses, behavioral problems, and cognitive deficits thought to reflect the most important morbidity in childhood OSA [33–39]. Psychiatric assessments included administration of the Computerized Diagnostic Interview Schedule for Children – Parent [40–42], and the Children's Psychiatric Rating Scale [43–45]. However, the final categorical diagnostic outcome variable was presence or absence of DSM-IV-defined ADHD, as determined by the interviewing clinician. This individual was a child psychiatrist, behavioral/developmental pediatrician, or child psychologist and in almost all cases, baseline and follow-up evaluations were performed by the same person.

A composite Behavioral Hyperactivity Index [46] (mean 50; standard deviation (s.d.) 10) was created from the average of the ADHD T-scores generated by each of two validated parental rating scales: the Conners' Parent Rating Scales [47] and the Child Symptom Inventory-4 [48] (or the Early Childhood Inventory-4 [49] for children between 3 and 5 years). Higher Behavioral Hyperactivity Indices indicated more significant symptoms. Cognitive testing lasted about 2 h and included the NEPSY [50], a developmental neuropsychological test battery designed for children aged 3–12 years. From the NEPSY, the Memory and Learning Score and the Attention/Executive Functions Score were averaged to generate a composite cognitive index (mean 100, s.d. 15; with higher scores indicating better performance). Children also completed the Continuous Performance Test-Second Edition (CPT-II or Kiddie CPT for children aged 3 or 4 years). The average of the omissions t score, commissions t score, and variability t score, on which higher scores are less desirable and normal means are 50, comprised the CPT outcome variable.

2.5. Analyses

Data were summarized as means ± s.d. when they showed normal distributions, and otherwise as medians with first and third quartiles. The primary explanatory variables were PLMI ≥ 5 and PLMAI ≥ 1, as the continuous variables PLMI and PLMAI where highly skewed. The former threshold (PLMI ≥ 5) is thought to have clinical meaning as a cut point above which leg movements can have clinical impact in children, and periodic limb movement disorder can be diagnosed [26]. Although no PLMAI threshold for abnormality is widely accepted, we used PLMAI ≥ 1 to identify children who had more of these events than did their peers. This cut point corresponds to the recommended one-event-per-hour threshold for diagnosis of OSA in children [26].

Outcome measures were provided by the assessments of insomnia, sleepiness, cognition, behavior, and mental health. Changes in each outcome, defined as the postoperative score minus the preoperative score, were tested for significance by paired *T* tests, Wilcoxon signed rank tests (for nonparametric continuous variables), or McNemar's tests. To assess the extent to which PLMI or PLMAI were associated with each concurrent neurobehavioral morbidity at baseline and again (separately) at follow-up, logistic regression models were used, except when outcome measures were normally distributed, in which case general linear models were used. A similar approach was used to compare changes in PLMI or PLMAI to changes in neurobehavioral outcomes. All regression models were adjusted for the following potential confounds, or changes in these variables where relevant: age, gender, body mass index z-score (BMI), socioeconomic level, and respiratory disturbance index. The level of significance was set at $p < 0.05$. Results were not adjusted for multiple comparisons, to maintain sensitivity in this novel effort to detect any possible associations between PLMS and neurobehavioral outcomes within a cohort not referred for specific concern about restless legs, PLMs, or mental health problems. Although PLMS are described at ages as young as 15 months [51], and periodic limb movement disorder is recognized as a useful diagnostic alternative to restless legs syndrome in children under 6 years old [52], fewer data are available to associate PLMS with neurobehavioral outcomes among these young children. Therefore, regression models were repeated after excluding children < 6 years old from the analyses. All analyses were performed with SAS 9.2 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Subjects and measures at baseline and follow-up

A total of 899 families with children scheduled for AT were approached about this research during a visit to their otolaryngologist's office. Among these, 147 families consented to participate and were evaluated before AT. Reasons that families cited when they declined to participate were most often lack of time, desire to avoid any additional stress around the time of surgery, or lack of interest in research. Among the 147 participating children, 144 underwent nocturnal polysomnography successfully with at least 6 h of recorded sleep, and an MSLT on the next day. These children provided the data for the analyses reported below. Among the 144 children, 137 (95%) were reassessed about 6 months after surgery, 7.2 ± 0.9 months after the initial testing.

Demographic and polysomnographic variables at baseline and follow-up are shown in Table 1. In general, the sample reflected mild to moderate pediatric OSA: 126 (88%) received AT for clinical indications that included suspected sleep-disordered breathing, and the baseline respiratory disturbance index was at least 1.0 for 132 (92%). After AT, OSA improved significantly, and BMI z scores increased as anticipated [53]. The sleep efficiency, arousal index, and sleep staging showed statistically significant improvements in this sizeable sample, but the magnitudes of the changes were generally small and of questionable clinical significance.

In contrast to OSA, PLMS became somewhat more common at follow up. After surgery, the proportion of subjects who had a PLMI ≥ 5 increased by one-half, from 10% to 15% of the sample ($p = 0.0067$). Among 12 subjects who had PLMI ≥ 5 before AT, 11 (92%) still met this criterion after AT. Among 125 subjects without PLMI ≥ 5 before AT, 10 (8%) newly met this criterion for the first time after AT (calculation limited to those subjects with follow-up assessments). Among eight subjects who had PLMAI ≥ 1 before AT, six (75%) still met this criterion after AT. Among 129 subjects without PLMAI ≥ 1 before AT, 12 children (9%) met this criterion for the first time after AT. Some number of PLMS were scored (i.e., PLMI > 0) on the baseline studies of 57 (40%) of the 144 subjects, and some number of PLMS with arousals were scored for 45 (31%). After AT, PLMS were noted on the baseline studies of 72 (53%) of the 137 subjects, and some number of PLMS with arousals were scored for 56 (41%). Overall, the PLMI and PLMAI before AT showed correlations of moderate strength with the PLMI and PLMAI after AT (rho = 0.43, $p < 0.0001$, and rho = 0.33, $p < 0.0001$, respectively).

Table 1
Demographic and polysomnographic data for participants.

	Pre-Adenotonsillectomy *N* = 144 No. (%), Median (Q1, Q3), or Mean ± SD	Post-Adenotonsillectomy *N* = 137 No. (%), Median (Q1, Q3), or Mean ± SD	*p**
Age (years)	7.1 ± 2.5	7.8 ± 2.5	NA
Male gender	81 (56%)	76 (55%)	NA
Body Mass Index z-score	0.63 ± 1.31	0.84 ± 1.05	<0.0001[a]
Socioeconomic class (at baseline only)	2.0 (2.0, 3.0)	NA	NA
Total Recording Time (TRT, min)	601 ± 38	607 ± 42	0.17[a]
Total Sleep Time (TST, min)	526 ± 51	540 ± 54	0.0061[a]
Sleep Efficiency (TST*100/TRT)	88 ± 7	89 ± 7	0.025[a]
Arousal index (events/hour of sleep)	11.1 (8.5, 14.4)	9.5 (7.8, 11.2)	<0.0001[b]
% Stage N1	12 ± 8	10 ± 3	0.0001[a]
% Stage N2	44 ± 7	47 ± 6	<0.0001[a]
% Stage N3	25 ± 5	23 ± 6	<0.0001[a]
% Stage R	19 ± 5	21 ± 4	0.0028[a]
Respiratory disturbance index (events/hour of sleep)	4.5 (2.0, 9.5)	1.5 (0.8, 2.6)	<0.0001[b]
Minimum oxygen saturation (%)	92 (89, 94)	93 (91, 94)	<0.0001[b]
Periodic Leg Movement Index (PLMI)	0.0 (0.0, 1.4)	0.4 (0.0, 2.0)	0.010[b]
Periodic Leg Movement Arousal Index (PLMAI)	0.0 (0.0, 0.1)	0.0 (0.0, 0.4)	0.0014[b]
Periodic Leg Movement Index ≥ 5	15 (10%)	21 (15%)	0.0067[c]
Periodic Leg Movement Arousal Index ≥ 1	10 (7%)	18 (13%)	0.0075[c]

* For change after adenotonsillectomy, among those subjects who had follow-up assessments.
[a] Paired T test.
[b] Wilcoxon signed rank test.
[c] McNemar's Test.

Outcome measures at baseline and follow-up are shown in Table 2. Missing data points, where noted, were mainly attributable to inability of the youngest children to perform the CPT. As with the sleep measures, outcome measures including those for insomnia symptoms, subjective sleepiness, objective sleepiness, hyperactive behavior, executive dysfunction, inattention, and diagnosis of ADHD all improved after AT, with the sole exception of inattention as reflected by the computerized continuous performance task. The magnitude of these changes ranged from small, for example on the MSLT, to robust, as reflected by subjective sleepiness, insomnia symptoms, executive dysfunction, and frequency of ADHD.

3.2. Are PLMS or PLMS with arousals associated with adverse concurrent morbidity?

Fully adjusted regression models showed that at baseline, PLMS (PLMI ≥ 5) were associated (inversely) with one or more sleepiness symptoms (odds ratio, OR = 0.29, 95% confidence interval, CI (0.09, 0.98)), but not with any of several other comorbidities: presence of one or more insomnia symptom (OR = 0.47 (0.14, 1.51)), low mean sleep latency (bottom quartile, ≤22 min, OR = 1.29 (0.36, 4.66)), high Behavioral Hyperactivity Index (≥65, OR = 0.92 (0.25, 3.41)), lower scores on the NEPSY Cognitive Index (beta = 0.19, se = 3.67, t = 0.05, p = 0.96), worse scores on the CPT (beta = –2.01, se = 2.96, t = –0.68, p = 0.50), or presence of ADHD (OR = 0.95 (0.29, 3.08)). For an unadjusted example, seven among 58 children with ADHD (12%) had PLMI ≥ 5, but so did eight among 86 children (9%) without ADHD. Similarly, in fully adjusted regression models, PLMS with arousals (PLMAI ≥ 1) were associated (inversely) with one or more sleepiness symptoms (OR = 0.12 (0.03, 0.51)), but not with one or more insomnia symptoms (OR = 0.35, (0.08, 1.51)), low mean sleep latency (bottom quartile, ≤22 min, OR = 1.50 (0.34, 6.63)), high Behavioral Hyperactivity Index (≥65, OR = 0.44 (0.08, 2.39)), lower NEPSY Cognitive Index (beta = –0.90, se = 4.21, t = –0.21, p = 0.83), poor scores on the CPT (beta = –4.15, se = 3.88, t = –1.07, p = 0.29), or presence of ADHD (OR = 0.53 (0.13, 2.20)). Associations were similarly nonsignificant, except for those with sleepiness symptoms, when PLMI and PLMAI were tested as continuous variables, instead of their dichotomized analogues, or when the analyses were confined to those subjects (n = 90) aged 6 or more years.

After AT, neither PLMI ≥ 5 nor PLMAI ≥ 1 were associated with any of the above measures of concurrent morbidity (all p > 0.10).

Table 2
Outcome measures – insomnia symptoms, subjective sleepiness, objective sleepiness, hyperactive behavior, executive dysfunction, inattention, and diagnosis of attention-deficit/hyperactivity disorder – before and after adenotonsillectomy.

	Pre-Adenotonsillectomy		Post-Adenotonsillectomy		*p**
	N	No. Positive (%), Median (Q1, Q3), or Mean ± SD	*N*	No. Positive (%), Median (Q1, Q3), or Mean ± SD	
Insomnia Scale (one or more of three symptoms)	144	73 (51%)	137	34 (25%)	<0.0001[c]
Sleepiness Scale (one or more of four symptoms)	144	117 (81%)	137	53 (39%)	<0.0001[c]
Mean Sleep Latency on Multiple Sleep Latency Test (min)	144	25.7 (22.2, 29.5)	137	26.5 (23.8, 29.9)	0.022[b]
Behavioral Hyperactivity Index (BHI)	137	55.0 (48.0, 66.5)	135	50.0 (46.0, 59.5)	<0.0001[b]
NEPSY Cognitive Index (CI)	137	101.4 ± 13.0	135	109.9 ± 12.1	<0.0001[a]
Continuous Performance Test	124	56.6 ± 8.6	112	55.5 ± 9.2	0.12[a]
Attention-Deficit/Hyperactivity Disorder (Proportion with diagnosis)	144	58 (40%)	137	31 (23%)	<0.0001[c]

* For change after adenotonsillectomy, among those subjects who had follow-up assessments.
[a] Paired T test.
[b] Wilcoxon signed rank test.
[c] McNemar's Test.

Table 3
Regression of changes in sleep and neurobehavioral outcome measures, after adenotonsillectomy, on new emergence of periodic leg movements (PLMI ≥ 5)*.

Outcome Variable	Overall Model		Emergence of PLMI ≥ 5 (within context of overall model)			
	R^2	p	Beta	S.E.	T or Wald Chi-Square	p
Insomnia Scale (one or more of three symptoms)	0.058	0.243	–0.19	0.10	–1.92	0.057
Sleepiness Scale (one or more of four symptoms)	0.052	0.313	0.19	0.11	1.71	0.090
Mean Sleep Latency on Multiple Sleep Latency Test (min)	0.083	0.076	–0.80	1.51	–0.53	0.598
Behavioral Hyperactivity Index (BHI)	0.070	0.180	–1.20	2.86	–0.42	0.676
NEPSY Cognitive Index (CI)	0.074	0.145	–7.64	3.36	–2.27	0.025
Continuous Performance Test	0.033	0.749	2.04	2.89	0.71	0.482
Attention-Deficit/Hyperactivity Disorder (Proportion with diagnosis)	0.022	0.820	0.62	0.77	0.66	0.417

* Results of general linear models, or a logistic regression model (for attention-deficit/hyperactivity disorder), after adjustment for age, gender, change in body mass index z-score, socioeconomic status, and change in respiratory disturbance index.

Table 4
Regression of changes in sleep and neurobehavioral outcome measures, after adenotonsillectomy, on new emergence of periodic leg movements with arousals (PLMAI ≥ 1)*.

Outcome Variable	Overall Model		Emergence of PLMAI ≥ 1 (within context of overall model)			
	R^2	p	Beta	S.E.	T or Wald Chi-Square	p
Insomnia Scale (one or more of three symptoms)	0.035	0.591	–0.05	0.09	–0.61	0.541
Sleepiness Scale (one or more of four symptoms)	0.039	0.519	0.10	0.10	1.01	0.313
Mean Sleep Latency on Multiple Sleep Latency Test (min)	0.082	0.081	–0.40	1.36	–0.30	0.768
Behavioral Hyperactivity Index (BHI)	0.070	0.179	–1.13	2.64	–0.43	0.669
NEPSY Cognitive Index (CI)	0.093	0.059	–8.70	3.10	–2.80	0.006
Continuous Performance Test	0.031	0.775	–1.41	2.56	–0.55	0.582
Attention-Deficit/Hyperactivity Disorder (Proportion with diagnosis)	0.029	0.681	0.91	0.67	1.83	0.176

* Results of general linear models, or a logistic regression model (for attention-deficit/hyperactivity disorder), after adjustment for age, gender, change in body mass index z-score, socioeconomic status, and change in respiratory disturbance index.

Similarly, after AT, neither PLMI nor PLMAI (as continuous variables) were associated with any concurrent morbidity measure (all $p > 0.10$). Results were no different when analyses were confined to subjects aged 6 or more years.

3.3. Are changes in PLMS or PLMS with arousals associated with changes in comorbidities after AT?

In fully adjusted regression models, children who had PLMI < 5 before AT but PLMI ≥ 5 after AT ($n = 10$) in comparison to the other children studied before and after AT ($n = 127$) showed no significant worsening of insomnia symptoms, sleepiness symptoms, mean sleep latency on MSLTs, Behavioral Hyperactivity Index, CPT scores, or tendency to resolve an initial diagnosis of ADHD (Table 3). Results were similar when the analysis was confined to $n = 5$ versus $n = 81$ such subjects aged 6 years or older, though some of the models may not have been reliable with such small numbers of subjects in the first group. Children who had PLMI < 5 before AT but PLMI ≥ 5 after AT, in comparison to other children, did experience less improvement on the NEPSY Cognitive Index. Parallel results emerged when PLMAI ≥ 1, newly detected for $n = 12$ children after surgery, was tested in place of PLMI ≥ 5 (Table 4). Results were similar when pre-to-post AT changes in PLMI and PLMAI were used as continuous rather than dichotomous variables in regression models (data not shown). Figures 1 and 2 do show that the changes in NEPSY scores were associated with PLMI and PLMAI, respectively, but in both cases, a few outliers with extreme changes in PLMI or PLMAI appeared likely to drive the weak associations that nonetheless achieved significance.

Discussion

This study of 144 children scheduled for AT combined gold-standard sleep laboratory assessments with intensive evaluations of neurobehavioral morbidity to show that PLMS, with or without arousal, are fairly common at baseline and more common after surgery, but appear unlikely at either time point to have a strong clinical impact. Among the 137 children studied both before and after AT, the frequency of PLMS sufficient to meet polysomnographic criteria for periodic limb movement disorder increased by 50%.

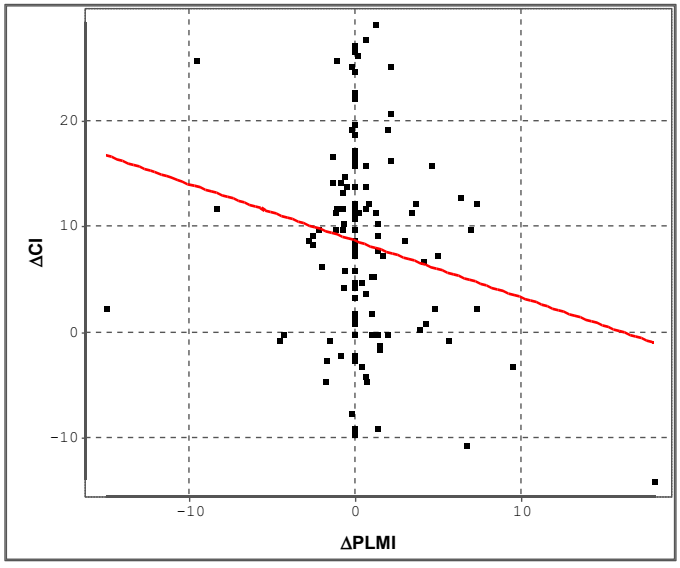

Fig. 1. The change in the NEPSY Cognitive Index (ΔCI) after adenotonsillectomy is plotted against the change in the periodic leg movement index (ΔPLMI). $R^2 = 0.037$, $p = 0.030$. The few outliers with more extreme changes in PLMI were likely to be influential, as a nonparametric Spearman correlation coefficient did not confirm a significant association (rho = –0.11, $p = 0.23$).

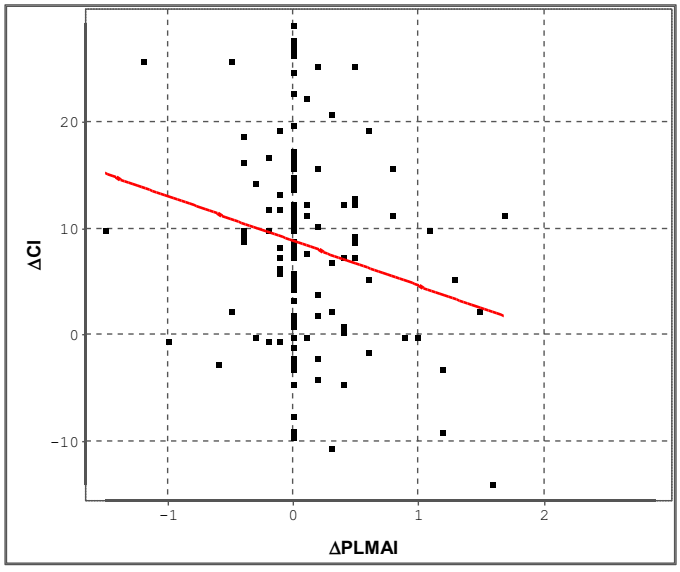

Fig. 2. The change in the NEPSY Cognitive Index (ΔCI) after adenotonsillectomy is plotted against the change in the periodic leg movement with arousal index (ΔPLMAI). $R^2 = 0.044$, $p = 0.017$. The few outliers with more extreme changes in PLMAI were likely to be influential, as a nonparametric Spearman correlation coefficient did not confirm a significant association (rho = –0.14, $p = 0.11$).

However, neither PLMS nor PLMS with arousals predicted worse concurrent morbidity, with respect to insomnia symptoms, sleepiness symptoms, objective sleepiness on an MSLT, parental ratings for hyperactivity, an objective test of attention, or qualification for diagnosis of ADHD. Analyses of changes in PLMS or PLMS with arousals, versus changes in several sleep complaints and neurobehavioral measures, showed no statistically significant associations (with only one possible exception) that might support biological cause-and-effect relationships between the leg movements and the outcomes studied. These findings are especially interesting in the context of previous literature on PLMS among patients with sleep-disordered breathing, and patients studied before and after treatment for sleep apnea, in the context of ADHD, and in childhood in particular.

We previously reported that on full polysomnography, among 1124 referred adults with suspected or confirmed OSA, 24% had PLMI ≥ 5 [3]. Although referred children are thought to have PLMS less commonly, figures have ranged widely, including for example 6% of 591 children [54], 10% of 101 children [55], and 23% of 252 children [51]. Children with sickle cell disease, narcolepsy, and some other specific disorders may have PLMS more frequently than the snoring children commonly referred to sleep disorders centers [56,57]. Our finding of a 10% frequency among children scheduled for AT, if generalizable to the 500,000 adenotonsillectomies performed annually in the US [58], suggest that about 50,000 of these children would demonstrate PLMI ≥ 5 preoperatively, and 7 months later, 75,000 may have PLMS at a frequency thought to have potential impact.

Therefore, a key question is whether PLMI ≥ 5 is in fact clinically significant. Pediatric OSA is associated with a wide range of adverse outcomes [59]. Although AT almost always improves sleep apnea, baseline morbidity does not always resolve [46]. Investigators have hypothesized that to an extent PLMS may be more common after sleep apnea is treated, and they could explain persistent neurobehavioral morbidity [60]. However, our findings now suggest that PLMS in this setting are unlikely to have these consequences. At baseline, no outcome measures were worse in association with PLMS or PLMS with arousals. Conversely, the PLMS and especially PLMS with arousals did predict a lower rather than higher likelihood of sleepiness, in parallel with previous findings from adults [2,3]. When PLMS occur, less sleepy individuals may be more easily aroused. Arousals more often precede than follow PLMS [61], and can occur exactly when expected within a series of PLMS even when a leg movement fails to materialize [62]. Some have argued that the clinical significance of PLMS outside the context of specific neurological conditions associated with PLMS – mainly those conditions that involve abnormal dopaminergic transmission – may be negligible [63,64].

Our findings on follow-up after AT further support this conclusion. Although the frequency of children with PLMI ≥ 5 increased by 50%, still no association with concurrent neurobehavioral morbidity or sleepiness could be identified. Absence of relationships between changes in PLMS or PLMS with arousals and changes in neurobehavioral morbidity failed to support a significant biological cause-and-effect relationship between the leg movements and the putative outcomes. Tables 3 and 4 show that newly developed PLMS or PLMS with arousals were associated with few changes in outcome measures after surgery, in each case to an extent that was clinically negligible in magnitude.

Previous studies that have focused on children referred with ADHD, or periodic limb movement disorder (PLMI ≥ 5 with relevant sleep symptoms), have emphasized close connections between these conditions [4–8]. However, findings may have been influenced by referral bias, as patients with both sleep and behavioral problems may be referred to specialists known for expertise at their intersection. Current findings also contrast with our own previous data, for example from surveys administered in general pediatric waiting rooms [65], or from a large sleep laboratory where referrals are not linked to clinicians with any specific interest [66]. The present study, with more in-depth, gold-standard assessments of neurobehavioral outcomes, could not confirm similar associations between PLMS and behavior.

Our current data appear to be the first to show an increase in PLMS, well after adenostonsillectomy. Previous studies of PLMS among adults treated for OSA have shown variable results and, as noted above, were usually performed during an initial night of continuous positive airway pressure (CPAP) titration, before habituation to nightly therapy or more permanent treatment by surgery. One study of 14 adults with PLMI ≥ 5 on repeat polysomnography, several months after home use of CPAP, did show that the PLMI had increased from baseline [9].

Exactly why PLMS would increase after treatment for OSA remains uncertain. Some authors have speculated that treatment of sleep apnea might unmask occult PLMS [12]. A leg movement that could qualify as a PLM, especially when associated with an arousal, is often followed by transient depression in respiration that could qualify as an hypopnea; in such cases, scoring rules require that the hypopnea, rather than the putative PLM, be scored [19]. Thus, elimination of hypopneas could lead to recognition that underlying PLMS are present. However, we were unable to replicate the previous observation [12] that the baseline respiratory disturbance index correlated with the PLMI at follow-up (data not shown). Others have speculated that CPAP may induce PLMS in children [60]. Although this remains possible, it does not explain why our subjects would have increased PLMS 6 months after AT.

Strengths of the current study include its novel focus on PLMS in the setting in which they are most often discovered, among children at risk for OSA. This study capitalized on gold-standard sleep laboratory measures; longitudinal if not randomized data; a high rate of successful follow-up at 6 months; well-validated, rigorous neurobehavioral assessments; recording of PLMS in individual legs; a stable recording rather than a CPAP titration with changing conditions; and follow-up well after treatment for OSA has

been established. The sample size was sizeable. Although only a minority of children had PLMI ≥ 5 or PLMAI ≥ 1, the sample was sufficient to replicate previous suggestions that PLMS can be weakly associated with fewer sleepiness complaints [2,3]. Numbers of subjects with new, postoperative PLMS or PLMS with arousals were sufficient to detect an association, with NEPSY changes, that explained <10% of their variance. Other associations that might have reached significance in an even larger sample might similarly have failed to explain a clinically meaningful proportion of the relevant outcomes.

Limitations of this study do include the absence of more rigorous, recently suggested approaches to PLMS scoring [67] that might have helped distinguish PLMS related to restless leg syndrome from PLMS arising for other reasons. We recorded PLMS for only one night, before and after surgery. Although the one-night protocol replicated data that can be obtained in clinical practice, night-to-night variability in PLMS could have limited our ability to identify correlates with neurobehavioral outcomes. Use of esophageal pressure monitoring conceivably could have disrupted sleep and fostered PLMS. However, previously published data from our laboratory, on 290 adults and 20 children, suggested no clinically significant effects on scored sleep and no statistically significant effects on PLMS [68]. In the present study, we did not assess outcomes other than cognition, behavior, sleepiness, and symptoms. Periodic leg movements can be associated with high blood pressure [69] and perhaps other outcomes that were not assessed. An observational study design cannot prove that AT actually causes increased PLMS. Finally, only 16% of families approached about this study agreed to participate. Although this level of participation resembles that found in many clinical studies that demand significant time and effort from subjects and their families, findings from this study, especially where they concern observed frequencies rather than associations or intra-subject changes, may not be generalizable to all children who undergo AT.

Nonetheless, current results do suggest several implications for clinical practice. The frequency of PLMS before and especially after treatment for OSA raises the question of whether laboratory-based sleep studies to detect PLMS should be considered more often than they are now. However, at the same time, this study provides little if any evidence that for children in this setting, PLMS are likely to have detrimental impact on cognition, behavior, sleep, or sleepiness. Clinicians who see patients back with persistent sleep-related concerns after AT should consider PLMS. However, further research will be needed to clarify exactly what adverse consequences, if any, arise from these polysomnographic findings.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.05.004.

Acknowledgements

The investigators are grateful to the patients and families who volunteered considerable time and effort, and to the surgeons and staff who identified these participants at the clinics of the University of Michigan Division of Pediatric Otolaryngology and the Michigan Otolaryngology Surgery Associates. Surgeons who assisted at the University of Michigan included Drs. Charles Koopmann, Marci Lesperance, Glenn Green, Marc Thorne, and Susan Garetz. Surgeons who assisted at the Michigan Otolaryngology Surgery Associates included Drs. Thomas Weimert, Ronald Bogdasarian, Paul Hoff, and Laurence Ho.

References

[1] Berry RB, Brooks R, Gamaldo CE, Harding SM, Marcus CL, Vaughn BV. The AASM manual for the scoring of sleep and associated events: rules, terminology and TEchnical specifications. Darien, Illinois: American Academy of Sleep Medicine; 2012.
[2] Mendelson WB. Are periodic leg movements associated with clinical sleep disturbance? Sleep 1996;19:219–23.
[3] Chervin RD. Periodic leg movements and sleepiness in patients evaluated for sleep-disordered breathing. Am J Respir Crit Care Med 2001;164:1454–8.
[4] Picchietti DL, England SJ, Walters AS, Willis K, Verrico T. Periodic limb movement disorder and restless legs syndrome in children with attention-deficit-hyperactivity disorder. J Child Neurol 1998;13:588–94.
[5] Picchietti DL, Underwood DJ, Farris WA, Walters AS, Shah MM, Dahl RE, et al. Further studies on periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. Mov Disord 1999;14:1000–7.
[6] Picchietti DL, Walters AS. Restless legs syndrome and periodic limb movement disorder in children and adolescents: comorbidity with attention-deficit hyperactivity disorder. Child Adolesc Psychiatry Clin N Am 1996;5:729–40.
[7] Picchietti DL, Walters AS. Severe periodic limb movement disorder in childhood and adolescence. Sleep Res 1996;25:333.
[8] Picchietti DL, Walters AS. Moderate to severe periodic limb movement disorder in childhood and adolescence. Sleep 1999;22:297–300.
[9] Fry JM, DiPhillipo MA, Pressman MR. Periodic leg movements in sleep following treatment of obstructive sleep apnea with nasal continuous positive airway pressure. Chest 1989;96:89–91.
[10] Yamashiro Y, Kryger MH. Acute effect of nasal CPAP on periodic limb movements associated with breathing disorders during sleep. Sleep 1994;17:172–5.
[11] Hedli LC, Christos P, Krieger AC. Unmasking of periodic limb movements with the resolution of obstructive sleep apnea during continuous positive airway pressure application. J Clin Neurophysiol 2012;29:339–44.
[12] Baran AS, Richert AC, Douglass AB, May W, Ansarin K. Change in periodic limb movement index during treatment of obstructive sleep apnea with continuous positive airway pressure. Sleep 2003;26:717–20.
[13] Kohler MJ, Lushington K, van den Heuvel CJ, Martin J, Pamula Y, Kennedy D. Adenotonsillectomy and neurocognitive deficits in children with Sleep Disordered Breathing. PLoS ONE 2009;4:e7343.
[14] Scholle S, Scholle HC, Zwacka G. Periodic leg movements and sleep-disordered breathing in children. Somnologie 2001;5:153–8.
[15] Chervin RD, Ruzicka DL, Hoban TF, Fetterolf JL, Garetz SL, Guire KE, et al. Esophageal pressures, polysomnography, and neurobehavioral outcomes of adenotonsillectomy in children. Chest 2012;142:101–10.
[16] Chervin RD, Garetz SL, Ruzicka DL, Hodges EK, Giordani BJ, Dillon JE, et al. Do respiratory cycle-related EEG changes or arousals from sleep predict neurobehavioral deficits and response to adenotonsillectomy in children? J Clin Sleep Med 2014 (in press).
[17] Weatherly RA, Mai EF, Ruzicka DL, Chervin RD. Identification and evaluation of obstructive sleep apnea prior to adenotonsillectomy in children: a survey of practice patterns. Sleep Med 2003;4:297–307.
[18] Hollingshead AB. Two factor index of social position. New Haven: Yale Press; 1965.
[19] Iber C, Ancoli-Israel S, Chesson A, Quan SF. For the American Academy of Sleep M. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, Illinois: American Academy of Sleep Medicine; 2007.
[20] Kushida CA, Giacomini A, Lee MK, Guilleminault C, Dement WC. Technical protocol for the use of esophageal manometry in the diagnosis of sleep-related breathing disorders. Sleep Med 2002;3:163–73.
[21] Chervin RD, Ruzicka DL, Wiebelhaus JL, Hegeman GL 3rd, Marriott DJ, Marcus CL, et al. Tolerance of esophageal pressure monitoring during polysomnography in children. Sleep 2003;26:1022–6.
[22] Littner MR, Kushida C, Wise M, Davila DG, Morgenthaler T, Lee-Chiong T, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test – An American Academy of Sleep Medicine Report – Standards of practice committee of the American Academy of Sleep Medicine. Sleep 2005;28:113–21.
[23] Gozal D, Wang M, Pope DW Jr. Objective sleepiness measures in pediatric obstructive sleep apnea. Pediatrics 2001;108:693–7.
[24] Golan N, Suraya S, Pillar G. Daytime sleepiness in children with attention deficit hyperactive disorder. Sleep 2003;26(Abstract Suppl.):A127.
[25] Hoban TF, Chervin RD. Assessment of sleepiness in children. Semin Pediatr Neurol 2001;8:216–28.
[26] American Academy of Sleep M. International classification of sleep disorders, 2nd ed. Diagnostic and coding manual. Westchester, Illinois: American Academy of Sleep Medicine; 2005.
[27] Sheldon SH. Disorders of initiating and maintaining sleep. In: Sheldon SH, Ferber R, Kryger MH, editors. Principles and practice of pediatric sleep medicine. Elsevier Saunders; 2005. p. 127–60.
[28] Archbold KH, Pituch KJ, Panahi P, Chervin RD. Symptoms of sleep disturbances among children at two general pediatric clinics. Journal of Pediatrics 2002;140:97–102.
[29] Chervin RD, Archbold KH, Panahi P, Pituch KJ. Sleep problems seldom addressed at two general pediatric clinics. Pediatrics 2001;107:1375–80.

[30] Chervin RD, Hedger KM, Dillon JE, Pituch KJ. Pediatric Sleep Questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. Sleep Med 2000;1:21–32.
[31] Chervin RD, Weatherly RA, Garetz SL, Ruzicka DL, Giordani BJ, Hodges EK, et al. Pediatric sleep questionnaire: prediction of sleep apnea and outcomes. Arch Otolaryngol Head Neck Surg 2007;133:216–22.
[32] Chervin RD, Weatherly RA, Ruzicka DL, Burns JW, Giordani BJ, Dillon JE, et al. Subjective sleepiness and polysomnographic correlates in children scheduled for adenotonsillectomy vs. other surgical care. Sleep 2006;29:495–503.
[33] Guilleminault C, Korobkin R, Winkle R. A review of 50 children with obstructive sleep apnea syndrome. Lung 1981;159:275–87.
[34] Guilleminault C, Winkle R, Korobkin R, Simmons B. Children and nocturnal snoring–evaluation of the effects of sleep related respiratory resistive load and daytime functioning. Eur J Pediatr 1982;139:165–71.
[35] Ali NJ, Pitson DJ, Stradling JR. Snoring, sleep disturbance, and behaviour in 4–5 year olds. Arch Dis Child 1993;68:360–6.
[36] Hansen DE, Vandenberg B. Neuropsychological features and differential diagnosis of sleep apnea syndrome in children. J Clin Child Psychol 1997;26:304–10.
[37] Ali NJ, Pitson D, Stradling JR. Sleep disordered breathing: effects of adenotonsillectomy on behaviour and psychological functioning. Eur J Pediatr 1996;155:56–62.
[38] Weissbluth M, Davis AT, Poncher J, Reiff J. Signs of airway obstruction during sleep and behavioral, developmental, and academic problems. Dev Behav Pediatr 1983;1983:119–21.
[39] Rhodes SK, Shimoda KC, Wald LR, O'Neil PM, Oexmann MJ, Collop NA, et al. Neurocognitive deficits in morbidly obese children with obstructive sleep apnea. J Pediatr 1995;127:741–4.
[40] Shaffer D, Fisher P, Dulcan MK, Davies M, Piacentini J, Schwab-Stone ME, et al. The NIMH diagnostic interview schedule for children version 2.3: description, acceptability, prevalence rates, and performance in the MECA study. J Am Acad Child Adolesc Psychiatry 1996;35:865–77.
[41] Halperin JM, Newcorn JH, Kopstein I, McKay KE, Schwartz ST, Siever LJ, et al. Serotonin, aggression, and parental psychopathology in children with attention-deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 1997;36:1391–8.
[42] Swanson JM, Wigal S, Greenhill LL. Analog classroom assessment of Adderall in children with ADHD. J Am Acad Child Adolesc Psychiatry 1998;37:519–26.
[43] Spencer EK, Alpert M, Pouget ER. Scales for the assessment of neuroleptic response in schizophrenic children: specific measures derived from the CPRS. Psychopharmacol Bull 1994;30:199–202.
[44] Overall JE, Campbell M. Behavioral assessment of psychopathology in children: infantile autism. J Clin Psychol 1988;44:708–16.
[45] National Institute of Mental H. Children's psychiatric rating scale – NIMH. Psychopharmacol Bull 1985;21:770.
[46] Chervin RD, Ruzicka DL, Giordani BJ, Weatherly RA, Dillon JE, Hodges EK, et al. Sleep-disordered breathing, behavior, and cognition in children before and after adenotonsillectomy. Pediatrics 2006;117:e769–78.
[47] Conners CK. Conners' rating scales – revised. North Tonawanda, NY: Multi-Health Systems Publishing; 1997.
[48] Gadow KD, Sprafkin J. Child symptom inventory-4. Stony Brook, N.Y.: Checkmate Plus; 1994.
[49] Sprafkin J, Gadow KD. Early childhood symptom inventory manual. Stony Brook, N.Y.: Checkmate Plus; 1996.
[50] Korkman M, Kirk U, Kemp S. A developmental neuropsychological assessment. San Antonio: Harcourt Brace Jovanovich; 1998.
[51] Martinez S, Guilleminault C. Periodic leg movements in prepubertal children with sleep disturbance. Dev Med Child Neurol 2004;46:765–70.
[52] Picchietti DL, Picchietti MA. Restless legs syndrome. In: Kothare SV, Kotagal S, editors. Sleep in childhood neurological disorders. New York: Demos Medical; 2011. p. 57–70.
[53] Amin R, Anthony L, Somers V, Fenchel M, McConnell K, Jefferies J, et al. Growth velocity predicts recurrence of sleep-disordered breathing 1 year after adenotonsillectomy. Am J Respir Crit Care Med 2008;177:654–9.
[54] Kirk VG, Bohn S. Periodic limb movements in children: prevalence in a referred population. Sleep 2004;27:313–15.
[55] Martin BT, Williamson BD, Edwards N, Teng AY. Parental symptom report and periodic limb movements of sleep in children. J Clin Sleep Med 2008;4:57–61.
[56] Rogers VE, Marcus CL, Jawad AF, Smith-Whitley K, Ohene-Frempong K, Bowdre C, et al. Periodic limb movements and disrupted sleep in children with sickle cell disease. Sleep 2011;34:899–908.
[57] Jambhekar SK, Com G, Jones E, Jackson R, Castro MM, Knight F, et al. Periodic limb movements during sleep in children with narcolepsy. J Clin Sleep Med 2011;7:597–601.
[58] Bhattacharyya N, Lin HW. Changes and consistencies in the epidemiology of pediatric adenotonsillar surgery, 1996–2006. Otolaryngol Head Neck Surg 2010;143:680–4.
[59] Marcus CL, Brooks LJ, Draper KA, Gozal D, Halbower AC, Jones J, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2012;130:576–84.
[60] Pai V, Khatwa U, Ramgopal S, Singh K, Fitzgerald R, Kothare SV. Prevalence of pediatric periodic leg movements of sleep after initiation of PAP therapy. Pediatr Pulmonol 2013;49:252–6.
[61] Karadeniz D, Ondze B, Besset A, Billiard M. EEG arousals and awakenings in relation with periodic leg movements during sleep. J Sleep Res 2000;9:273–7.
[62] El-Ad B, Chervin RD. The case of a missing PLM. Sleep 2000;23:450–1.
[63] Nicolas A, Lesperance P, Montplaisir J. Is excessive daytime sleepiness with periodic leg movements during sleep a specific diagnostic category? Eur Neurol 1998;40:22–6.
[64] Montplaisir J, Michaud M, Denesle R, Gosselin A. Periodic leg movements are not more prevalent in insomnia or hypersomnia but are specifically associated with sleep disorders involving a dopaminergic impairment. Sleep Med 2000;1:163–7.
[65] Chervin RD, Archbold KH, Dillon JE, Pituch KJ, Panahi P, Dahl RE, et al. Associations between symptoms of inattention, hyperactivity, restless legs, and periodic leg movements. Sleep 2002;25:213–18.
[66] Chervin RD, Archbold KH. Hyperactivity and polysomnographic findings in children evaluated for sleep-disordered breathing. Sleep 2001;24:313–20.
[67] Ferri R, Bruni O, Novelli L, Picchietti MA, Picchietti DL. Time structure of leg movement activity during sleep in attention-deficit/hyperactivity disorder and effects of levodopa. Sleep Med 2013;14:359–66.
[68] Chervin RD, Aldrich MS. Effects of esophageal pressure monitoring on sleep architecture. Am J Respir Crit Care Med 1997;156:881–5.
[69] Wing YK, Zhang J, Ho CK, Au CT, Li AM. Periodic limb movement during sleep is associated with nocturnal hypertension in children. Sleep 2010;33:759–65.